REMARKS

This paper is filed in response to the outstanding final official action dated July 7, 2009 (hereafter, the "official action") and notice of appeal dated January 7, 2010 (received by the Patent Office on January 12, 2010) in the above-referenced application. This paper is timely filed as it is accompanied by a petition for extension of time and authorization to charge our credit card account in the amount of the requisite fee. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed, or which should have been filed herewith to our Deposit Account No. 13-2855, under Order No. ANA-5955 (31203/30056).

Claims 1, 2, 4, 5, and 7-13 are pending. By the foregoing, claim 1 has been amended to positively recite a patient having a tissue that is subject to an ischemic event. Additionally, new claims 14 and 15 have been added. Support for new claims 14 and 15 may be found, for example, at page 6, line 16, and at page 7, line 4, respectively. No new matter has been added.

Claims 1, 2, 4, 5, and 7-13 remain rejected under 35 U.S.C. §103(a) as assertedly obvious over Saito *et al.*, *J. Cerebral Blood Flow Metabol.*, *17*:857-864 (1997) ("Saito") in view of Gray *et al.*, GB 2350297 ("Gray") and Gelb *et al.*, *Canadian Anaesth. Soc. J.*:*25(6)*:488-494 (Nov. 1978). The applicants respectfully traverse the rejections.

All pending claims recite a method of treating a patient having a tissue that is subject to an ischemic event comprising parenterally administering a sub-anesthetic amount of a formulation comprising a halogenated volatile anesthetic to a patient having a tissue that is subject to an ischemic event, wherein the sub-anesthetic amount is effective to improve the tissue's resistance to or tolerance of the ischemic event. The applicants respectfully submit that the cited references—whether taken alone or in any proper combination—do not render the claimed invention obvious because one of ordinary skill in the art would not have had the requisite motivation to combine Saito with Gray and/or Gelb. Further, one of ordinary skill would not have had a reasonable expectation of success based on the proposed extraordinary modifications of Saito.

Saito discloses administering to cats, via inhalation, 0.75% halothane in 70% nitrous oxide and 30% oxygen, which corresponds to an amount of halothane sufficient to maintain a general anesthetic effect. Saito further suggests that the aforementioned halothane administration provided some protective effect against left middle cerebral artery occlusion-induced brain ischemia — at least relative to the administration of α-chloralose (Saito did not

perform a placebo control after induction of MCAO and thus does not conclusively demonstrate a protective effect).

The Office acknowledged that "Saito et al do not teach parenteral administration of a halogenated volatile anesthetic, with an emulsification adjuvant and an emulsifier in a sub-anesthetic amount." *See* page 7 of the official action. Thus, the examiner turned to Gray, which discloses parenteral administration of an injectable halogenated anesthetic formulation, and Gelb, which discloses administration of sub-anesthetic amounts of halothane.

In order to have the requisite motivation to modify Saito in view of Gray, however, one of ordinary skill in the art would have had to have had a reasonable expectation that the injectable formulation disclosed in Gray would produce a protective effect against the left middle cerebral artery occlusion-induced brain ischemic insult model disclosed in Saito. The applicants respectfully submit that one of ordinary skill would not have had a reasonable expectation that the protective effect described in Saito, which was achieved via inhalation administration of halothane, could also be achieved by parenterally administering a formulation comprising a halogenated volatile anesthetic (such as halothane), as claimed. In support of this statement, the applicants respectfully submit that it is well known that one cannot presume that different routes of administration (of the same drug) achieve the same physiological effect. In this respect, Lucchinetti, *et al.*, *Int'l Anesthesia Res. Soc.*, *106(5)*:1346-1349 (May 2008)[1], when discussing emulsified intravenous isoflurane in comparison to inhaled isoflurane, unequivocally states:

> ...the route of administration are known to profoundly affect pharmacokinetic and/or dynamic properties of a drug, to modify the ratio between therapeutic activities versus toxicity (therapeutic index), and are even capable of evoking novel biological actions.

See Lucchinetti at the first full paragraph of page 1346. In view of the above teaching in the art that there can be profound differences in pharmacodynamic properties attributable to different routes of administration, one of ordinary skill would not have had a reasonable expectation of success based upon the proposed modification of Saito in view of Gray.

Moreover, both Saito and Gray are directed to methods of administering anesthetic doses and fail to disclose or suggest administration of sub-anesthetic doses. Further, Saito teaches in the Discussion section that any ischemic protective effect demonstrated therein is

[1] Lucchinetti *et al.* is attached hereto as Attachment A.

attributed to administration of an anesthetic amount of halothane by distinguishing between the awake and anesthetized states:

> *Compared with the awake state*, volatile anesthetics, including halothane and sevoflurane, reduce brain damage in animals subjected to transient focal cerebral ischemia.

See Saito at the second full paragraph of page 862 (emphasis added). In view of this explicit teaching, one of ordinary skill in the art would not have had a reasonable expectation that the protective effect demonstrated in Saito could be achieved by administration of a sub-anesthetic amount of a halogenated volatile anesthetic, as claimed. Rather, one of ordinary skill in the art would understand any protective effect disclosed in Saito to be inseparable from the anesthetic dose administered therein.

Gelb further highlights the inventive aspects of the claimed invention. Gelb discloses that administration of a sub-anesthetic dose of halothane reduced the ventilatory response to hypoxemia. One of ordinary skill would have no motivation to combine Gelb with Saito (and/or Gray) because the reduction of ventilation is undesirable in patients suffering from ischemia. In this respect, Gelb explicitly states that "[t]he absence of a normal response to hypoxia increases the severity and, therefore, the danger of hypoxic episodes." *See* Gelb at the second full paragraph of page 493. In view of this disclosure, the applicants respectfully submit that one of ordinary skill would not modify Saito (and/or Gray) in view of Gelb because ischemia is well understood to result in tissue hypoxia and Gelb cautions against the danger of administering a sub-anesthetic amount of halothane in patients subject to hypoxic episodes. In this respect, the applicants respectfully submit that Gelb actually *teaches away* from the claimed subject matter because it teaches against administering a sub-anesthetic amount of a formulation comprising a halogenated volatile anesthetic to a patient having a tissue that is subject to an ischemic event, as claimed.

Moreover, it is not clear why one of ordinary skill would be motivated to substitute a sub-anesthetic amount of a halogenated anesthetic for an anesthetic amount based on the teachings of Gelb in view of Saito's explicit distinction between the anesthetic and awake states discussed above.

Prima facie obviousness under § 103(a) is a legal conclusion—not a fact—based on underlying facts. *In re Rinehart*, 531 F.2d 1048, 1052 (CCPA 1976); *In re Kumar*, 418 F.3d 1361, 1365 (Fed. Cir. 2005) ("Determination of obviousness under 35 USC § 103 is a legal conclusion based on underlying facts."). The present response identifies facts rebutting the

alleged legal conclusion that the claimed invention is *prima facie* obvious. All of these facts must be evaluated along with the facts on which the legal conclusion was originally reached. Having requested reconsideration of the legal conclusion set forth in the official action, the Patent Office is obligated to address all of the evidence and base its forthcoming legal conclusion(s) on such evidence, uninfluenced by its earlier conclusions. *Rinehart*, 531 F.2d at 1052.

New Claims 14 and 15

New claims 14 and 15 are patentable at least for the reasons discussed above. Additionally, new claims 14 and 15 recite specific patient populations not contemplated or suggested by any of the cited references. While Saito arguably discloses a protective effect, any such protective effect was only shown relative to the administration of another anesthetic agent (chloralose). Therefore, Saito does not disclose or suggest a method of treating a patient having a tissue that is subject to an ischemic event comprising parenterally administering a sub-anesthetic amount of a formulation comprising a halogenated volatile anesthetic to a patient having a tissue that is subject to an ischemic event, wherein the sub-anesthetic amount is effective to improve the tissue's resistance to or tolerance of the ischemic event, wherein the patient is in need of cardioprotection or neuroprotection, as recited in new claims 14 and 15. With respect to claim 15, Saito explicitly discloses that "halothane is not ranked high on the scale of neuroprotectants." *See* Saito at the second full paragraph of page 862

Neither Gray nor Gelb addresses the foregoing deficiencies.

CONCLUSION

In view of the foregoing, reconsideration and withdrawal of the rejections and allowance of all pending claims.

Should the examiner wish to discuss the foregoing, or any matter of form or procedure in an effort to advance this application to allowance, the examiner is urged to contact the undersigned attorney.

Respectfully submitted,

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August 11, 2010

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